TITLE: Debridement Procedures for Managing Diabetic Foot Ulcers: A Review of Clinical Effectiveness, Cost-effectiveness, and Guidelines

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CONTEXT AND POLICY ISSUES

The rising prevalence of diabetes mellitus (DM) and associated complications represent a global public health care problem and financial burden.[1,2] The estimated prevalence of DM in Canada was 6.8% (2.4 million) in 2009, a 230% increase from estimates in 1998. Increasing prevalence and associated costs to Canada's publically funded healthcare system is projected to continue. As of 2010 the estimated economic burden of DM and its complications in Canada was $12.2 billion.[3] The most common chronic complication of DM is diabetic foot ulcers (DFUs), with a prevalence of four to ten percent among DM patients.[1,4] Several factors predispose DM patients to DFUs including long duration of diabetes, trauma, infection, poor glycemic control, improper footwear, old age, smoking, low socioeconomic status, and psychological factors, however neuropathy and peripheral vascular disease may be the most significant causative factors.[1] The presentation of DFUs varies considerably with underlying pathogenesis and with the presence or absence of infection and ischemia. Along with serious complications including wound infection, osteomyelitis, and cellulitis, DFU patients also suffer from complications associated with DM including nephropathy, retinopathy, ischemic heart disease, and cerebrovascular disease. Furthermore, the potentially preventable endpoint of untreated DFU is amputation, which is itself associated with immense social and psychological consequences, in addition to significant morbidity, mortality and financial impact on healthcare.[1,2]

Debridement is the removal of necrotic tissue, foreign debris, bacterial growth, callus, wound edge, and wound bed tissue from chronic wounds in order to stimulate the wound healing process. Stimulation of wound healing mediated by debridement is thought to occur by the conversion of a chronic non-healing wound environment to an acute healing environment through the removal of cells that are not responsive to endogenous healing stimuli.[5] Debridement is used commonly in standard wound treatment of DFUs.[3] Methods of debridement include surgery (sharp debridement), chemical debridement (antiseptics, polysaccharide beads, pastes), autolytic (hydrogels, hydrocolloids and transparent films), biosurgery (maggots), mechanical (hydrodebridement), and biochemical debridement (enzyme preparations).[5,6] Callus is a buildup of keratinized skin formed under conditions of repeated

pressure or friction and may contribute to ulcer formation by creating focal areas of high plantar pressure.[5,7] The debridement of callus has been proposed to be relevant for both treatment and prevention of DFU.[7]

The purpose of this report is to retrieve and review existing evidence of comparative clinical effectiveness of different methods of debridement for the treatment of DFUs. Additionally examined in this report is the clinical effectiveness for treatment and prevention of DFU using callus debridement. Cost-effectiveness, and existing debridement guidelines for the treatment of DFUs will also be reviewed.

RESEARCH QUESTIONS

1. What is the comparative clinical effectiveness of wound debridement procedures for the treatment of diabetic foot ulcers?

2. What is the clinical effectiveness of surgical callus debridement for the prevention and treatment of diabetic foot ulcers?

3. What is the cost-effectiveness of wound debridement for the treatment of diabetic foot ulcers?

4. What are the evidence-based guidelines regarding wound debridement for the treatment of diabetic foot ulcers?

KEY FINDINGS

This report identified evidence that autolytic (hydrogel) and enzymatic debridement (clostridial collagenase ointment) are more clinically effective wound debridement procedures for the treatment of diabetic foot ulcers than standard wound care. This is supported by RCTs with important limitations including a moderate to high risk of bias. No clinical effectiveness evidence was found for callus debridement for the prevention and treatment of diabetic ulcers. The cost-effectiveness data identified suggests that clostridial collagenase ointment is more cost-effective than saline moist gauze for the debridement of diabetic foot ulcers, however the cost-effectiveness analysis has some important limitations. No clear consensus was present in the identified guidelines regarding diabetic foot ulcer debridement. Three different guidelines contained recommendations for selecting autolytic debridement in the treatment of diabetic foot ulcers. Recommendations for selecting surgical, mechanical, larvae, conservative sharp wound debridement, and enzymatic debridement techniques were also identified. Two guidelines also recommended callus debridement for treatment and prevention of DFU without recommending a specific debridement technique.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014 August, Issue 8), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology

assessments, systematic reviews, meta-analyses, randomized controlled trials, economic studies, and guidelines. The search was limited to English language documents published between Jan 1, 2009 and August 12, 2014.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for inclusion, according to selection criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults (18+) with diabetic foot ulceration or callus either in a hospital or community care setting.
Intervention	Debridement of diabetic foot ulcer or callus to remove non-viable tissue.
Comparator	For wound debridement: autolytic, enzymatic, biologic (maggots), mechanical, surgical (deep or superficial), no debridement (standard wound care) For callus removal: no debridement (standard care)
Outcomes	Healing rate (% healed), time to healing, wound size, wound infection, formation of granulation tissue, lower limb amputation, safety (adverse effects). For callus debridement: prevention of ulceration
Study Designs	Health Technology Assessments (HTA)/ Systematic review (SR)/Meta-analysis (MA); Randomized controlled trials (RCTs); Economic evaluations; and Evidence-based Guidelines

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria, were duplicates, or were published prior to 2009. Studies were excluded if they evaluated debridement for non-diabetic wound types. Randomized controlled trials (RCTs) were excluded if they were a part of a subsequently published systematic review (SR). SRs were excluded if it, or the included RCTs, were part of a subsequently published SR. These exclusions avoided over-representation in this report of the trials included in SRs.

Critical Appraisal of Individual Studies

The quality of the included SR and MA were assessed using the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) tool.[10] The quality of the RCT included in this report was assessed using the Downs and Black checklist[11] and economic analyses were appraised using Drummond's Checklist.[12] Critical appraisal of included guidelines used the Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument.[13] For all critical appraisals the strengths and limitations were described narratively instead of assigning a numerical score.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search strategy initially identified 132 articles. One reviewer screened titles and available abstracts, after which 108 were excluded as they did not meet the inclusion criteria (Table 1); as a result, 24 full text articles were retrieved for review. Another seven articles found in the grey literature were of interest. Upon review of the full text articles, 19 studies were excluded from this report consisting of four studies that examined an irrelevant intervention, three that examined an irrelevant population, six that were non-systematic reviews, one that was a retrospective case-control study, and one study that had a more recent version available. Four systematic reviews were also excluded as they were included in a single more recent systematic review.[5,7,14-16] Overlapping reviews were avoided to prevent an over-representation of the trial data in this report. This overlap of included studies is summarized in Appendix 2, and references of potential interest therein are included in the bibliography.

After selection, 12 studies met the inclusion criteria for this report including one SR,[14] one MA,[17] two RCTs,[18,19] one RCT with a cost-effectiveness analysis (CEA),[20] and seven guidelines containing relevant recommendations.[3,8,9,21-24] A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart[25] describes the section procedure of the studies included in this review (Appendix 1).

Summary of Study Characteristics

Clinical Effectiveness

Included SR, MA, and RCT characteristics are tabulated in Appendix 3 Table 3.1.

Study design

The included SR, Braun et al., 2014,[14] indirectly reviewed 12 relevant debridement of DFU trials,[26-37] as examined in four previously published SRs.[5-7,38] The SR was published in 2014 and the trial data reviewed was published between 1996 and 2009.[14] One of the SRs included in Braun et al., 2014 contained an MA. The relevant statistically significant results of the MA were included in Braun et al., 2014 and in this report.[7,14] The included MA was published in 2013 and reviews data from four trials, one of which is an RCT.[17] The trials included in the MA were published between 2000 and 2009 and summarize data from 282 trial participants.[17]

This report also includes three RCTs,[18-20] one of which includes a CEA.[20] None of these RCTs were examined in an identified SR, MA or HTA and were published in 2011, 2013 and 2014.[18-20]

Population

The included SR, MA and RCTs all examine DFU specifically.[14,17-20] A broad patient population was included in the MA as it states specifically that no requirements regarding the definition of DFU or classification of the wound was used when including studies.[17] A more precise definition of DFU was also not present in the included SR.[14] The RCT with a CEA included patients 18 years or older using medication for type 1 or 2 DM with neuropathic foot ulcers with a size between 0.5 and 10 cm^2, present for at least one month.[20] The most recently published RCT from 2014 had the same inclusion criteria, however also excluded patients with an ankle

brachial index (ABI) ≤ 0.7, DFUs with any clinical signs or symptoms of infection, serum albumin < 2.0 g/dL, serum pre-albumin < 15 mg/dL, or HbA1c > 12%.[19] Patients were also excluded from this study for having a DFU not requiring debridement, uncontrolled bleeding disorder, infection with systemic toxicity, an ulcer that could not be offloaded, current osteomyelitis of the target foot, or sub-dermal tissue involvement.[19] Patient inclusion criteria in the oldest RCT, published in 2011, were DFUs older than four weeks, that were nonclinically infected, that contained necrotic tissue, and that were indicated for mechanical debridement.[18] Patients were excluded for a DFU greater in size than 25cm^2, a DFU that penetrated to a bone or joint, for osteomyelitis, an ABI < 0.8, the use of anticoagulants and immunosuppressive drugs, or for known allergies to chlorine present in the intervention.[18] A DFU was defined in this RCT as a full-thickness break of the epithelium distal to the medial and lateral malleoli.[18]

Intervention and Comparators

The included SR reviewed evidence for a variety of debridement methods, namely surgical debridement, hydrogels, larvae therapy, and hydrodebridement. The comparators in these studies are not well defined in the SR, however comparators for surgical debridement are referred to as standard wound care (SWC). The SR discusses current SWC that itself includes offloading, debridement, and assessment.[14] This SR also reviews evidence for a wide variety of other DFU therapies.[14] The MA specifically examined trial data for maggot debridement therapy (MDT). One trial included in the MA used a slightly different organism than the other included studies, *Lucilia cuprina* instead of *Lucilia sericata*, and also used subcutaneous insulin in both treatment arms. Comparators in the MA were hydrogel and SWC.[17] Two of the three RCTs included in this report examine clostridial collagenase ointment (CCO) (Santyl, Smith & Nephew, Hull, UK).[19,20] CCO is an enzymatic debrider thought to remove detritus without harming healthy tissue. This enzymatic action is then thought to contribute to the formation of granulation tissue and epithelialization of dermal ulcers, however the precise mechanism by which CCO is proposed to stimulate wound healing is not clearly understood.[20] Both RCTs compared CCO to saline moist gauze wound dressing (SMG) and debrided all ulcers during the trial when deemed medically necessary. All patients were also required to use an offloading boot or other appropriate device.[19,20] The third RCT examined the use of Dermacyn (Oculus Innovative Sciences Inc, Petaluma, CA), a superoxidized aqueous solution, with a hydrodebridement system, the Versajet lavage system (Smith & Nephew, London, England).[18] The comparator was Versajet hydrodebridement with a standard saline solution. It was hypothesized that bactericidal properties of the superoxidized aqueous solution would reduce bacterial load and aid wound healing of DFUs treated with hydrodebridement.[18] None of the identified clinical effectiveness studies looked specifically at surgical callus debridement.

Outcomes

The outcomes examined in the SR included in this report were DFU healing efficacy and time to heal.[14] The MA extracted data from four MDT trials on DFU healing efficacy, time to heal, antibiotic usage, amputation, and infection incidence.[17] The two RCTs examining CCO treatment of DFUs had outcomes of wound assessments, change in ulcer area, and adverse events.[19,20] One CCO RCT also examined time to heal,[19] while the other had data on health economic outcomes (see cost-effectiveness).[20] The hydrodebridement RCT evaluated ulcer bacterial load, change in ulcer area, reduction in necrotic tissue, and adverse events.[18]

Cost-effectiveness

Characteristics of the included economic analyses are tabulated in Appendix 3, Table A3.2.

Study design

The included CEA was part of an included RCT examining enzymatic debridement with CCO.[20] This CEA was performed from the perspective of the Centers for Medicare and Medicaid Services (USA) as a payer. Costs were calculated for a four week treatment course and an eight week follow-up. Follow-up visit costs, including nursing and physician time, were accounted for, however it is not clear if other DFU treatment costs, such as offloading were part of this analysis.[20]

Patient Population and Comparison

Basing the analysis on the included RCT, the CEA compared CCO with SMG with 48 DFU patients that were 18 years or older. Patients were also using medication for type 1 or 2 DM with neuropathic DFUs present for at least one month, between 0.5 and 10 cm^2 in size. Both study arms were also treated with selective sharp debridement, when deemed medically necessary, and off-loading.[20]

Outcomes

In addition to clinical effectiveness outcomes of the RCT, the CEA aspect of the included article evaluated the cost per responder, the costs of the selective sharp debridement, and the costs of treatment associated evaluation and management. All costs are evaluated for the setting of a physician's office and also for treatment and management in a wound care facility.[20]

Assumptions

The CEA assumed equal costs for DFU cover dressings. The cost of CCO was based upon the proper use of the product not upon actual usage data. The study also did not account for cost discounting.[20]

Guidelines and Recommendations

Included guideline characteristics are tabulated in Appendix 3, Table A3.3.

Origin of Guidelines

Two sets of included guidelines originated in Canada. Both guidelines were published in 2013.[3,21] One guideline is from the Canadian Association for Enterostomal Therapy,[21] and one is from the Canadian Diabetes Association (CDA).[3] Three guidelines are from the USA: two are Agency for Healthcare and Research Quality (AHRQ) summaries of existing guidelines - one from the Wound, Ostomy, and Continence Nurses Society (WOCN),[8] and one from ConvaTec.[22] The third US guideline is from the Infectious Diseases Society of America (IDSA).[9] The other two guidelines are from the National Health and Medical Research Council (NHMRC) in Australia,[24] and the National Institute for Health and Clinical Excellence in the UK.[23] Three of the guidelines were published in 2013,[3,21,22] two were published in 2012,[8,9] and two were published in 2011.[23,24]

Interventions

All of the included guidelines in this report contain recommendations regarding debridement for the treatment of DFU.[3,8,9,21-24] Guidelines were identified for the use of the following debridement methods; autolytic,[22] enzymatic,[22] sharp debridement,[9,22,24] conservative sharp wound debridement (CSWD),[21] callus debridement,[8,9] larval,[9] mechanical,[9] and hydrogel.[24] CSWD was defined as removal of loose, devascularized tissue with the aid of scalpel, scissors or curette above the level of viable tissue and is a less extensive and aggressive procedure than surgical sharp debridement.[21] Three guidelines did not refer to a specific method of debridement in recommendations.[3,8,23]

Grading of Recommendations and Levels of Evidence

Two AHRQ summaries of guidelines, one from ConvaTec and one from WOCN, graded recommendations from A to C and levels of evidence from I to VI.[8,22] Guidelines authored by Rodd-Nielsen et al. did not grade recommendations but assigned a level of evidence from Ia to IV.[21] CDA graded recommendations from A to D and assigned a level of evidence from 1A to 4.[3] Guidelines from the IDSA graded recommendations as either Strong or Weak and assigned a level of evidence as High-quality, Moderate-quality, Low-quality or Very low-quality.[9] Recommendations were graded A to D or expert opinion (EO) and levels of evidence were assigned as I to IV in guidelines from NHMRC.[24] Guidelines from NICE did not grade recommendations, but assigned a Grading of Recommendations Assessment, Development and Evaluation (GRADE) level of evidence from High to Very Low.[23] Grading schemes used to grade recommendations and assign levels of evidence for the included guidelines are summarized in Appendix 4.

Summary of Critical Appraisal

The SR in this report, Braun et al., 2014, assessed the quality of included studies, outlined the data extraction methodology, included a PRISMA flowchart, a COI statement, and tabulated study conclusions. The SR also contained an outline of a literature search of multiple databases, filtered to retrieve SRs, MAs and RCTs published in English. The selection methodology was described and done independently in duplicate. This SR had limitations including unquantified conclusions, no assessment of publication bias, no description of the patient characteristics, no mention of adverse events or COI of included studies.[14] This SR summarized the included quality of evidence available on debridement for the treatment of DFU as moderate. This ranking is based on the American College of Physicians (ACP) criteria, and a moderate quality ranking is represented by RCT evidence with important methodological limitations or very strong evidence from observational studies. The largest SR included in Braun et al., concluded that the RCTs on debridement of DFUs were in general small, of poor methodological quality, and all contained an unclear risk of selection, performance, and detection bias.[7] The SR also reported industry support of one author.[14]

The included MA was of a high quality but was limited by the identified data.[17] The literature search and selection strategy was described and was comprehensive. The analyzed data of the MA had evidence of potential publication bias, was from small studies, only one study was an RCT, and the studies contained heterogeneous patient classification. The MA also reported that the RCT had a risk of selection, performance, and detection bias due to a lack of, or unclear, sequence generation, allocation concealment, and blinding.[17] One SR also reported that this same RCT on MDT was only available as an abstract, reported follow-up data only at ten days

while the trial was reported to be 30 months.[7] The remaining included studies in the MA were case-controlled studies.[17] Despite these limitations the MA had a statement of no financial COI, a PRISMA flowchart, a predefined objective, described all statistical methods, had quantified conclusions, and an explicit discussion on the limitations of the MA. These acknowledged limitations of the MA included the small number of studies, the limitation to English language studies, and the study heterogeneity with regards to wound aetiology and methodology. The MA did not examine adverse event data.[17] A summary of the critical appraisal of the included SR and MA using the AMSTAR tool[10] is available in Appendix 5, Table A5.1.

All of the identified RCTs were industry funded studies.[18-20] Two of the RCTs had the same industry funding and examined the same commercial CCO product, Santyl (Smith & Nephew, Hull, UK).[19,20] These trials were of similar quality and one of these RCTs also contained some health economic data.[20] Both CCO RCTs were open-label trials prone to bias due to a lack of allocation concealment. Neither trial presented data on debridement decisions or objective criteria for debridement decisions that were deemed medically necessary. The impact of debridement on the outcome of wound surface area was not discussed. These trials were both registered trials, with clear patient eligibility criteria, used a well described wound assessment tool, tabulated patient and ulcer characteristics with no statistically significant differences between groups, outlined a randomization method, described the statistical methods used, described the intervention, described the outcome assessment and presented adverse event data.[19,20] The other included RCT was also an industry sponsored study examining the clinical effectiveness of a particular commercial product, Dermacyn (Oculus Innovative Sciences Inc., Petaluma, CA).[18] This study lacked a description of allocation concealment and blinding assessment methodology however the study described itself as a prospective, two-center, randomized, controlled, double-blind study.[18] One outcome assessment method was inadequately described, and the clinical relevance of the bacterial load outcome was not established.[18] The strengths of this trial were the tabulation of patient and ulcer characteristics with no obvious differences between groups, the clear patient eligibility criteria, the randomization method was described, and adverse event outcomes were mentioned.[18] A critical appraisal summary of the included RCTs using the Downs and Black checklist[11] is tabulated in Appendix 5, Table 5.2.

The one included CEA used data from an RCT published in the same article.[20] The RCT was an open-label trial with limited long term data and endpoints available for the CEA. Additionally the CEA did not conduct any sensitivity analyses. This CEA did have a well-defined analysis, a clear purpose, and a relevant comparator. A significant driver of the difference in cost of the treatment arms was the requirement for surgical debridement during the trial. No data on debridement decisions or objective criteria for debridement decisions was reported. The analysis included the characteristics of the patients from the trial, and a breakdown of the costs was provided along with the source of those costs. The assumptions made for the analysis were appropriate although the actual usage data of the intervention might have been more informative than assuming optimal usage.[20] This appraisal is summarized in Appendix 5, Table 5.3.

Included guidelines varied in quality. Two of the seven identified guidelines offer a Canadian perspective.[3,21] Five guidelines have graded recommendations for debridement in the treatment of DFUs.[3,8,9,22,24] One guideline linked ungraded recommendations to a level of evidence,[21] two guidelines had graded recommendations presented next to the evidence level used to support it,[3,9] and three guidelines had recommendation grades that were directly dependent on the level of evidence.[8,22,24] The included guidelines varied in the reporting and existence of potential

COIs; two guidelines provided a statement of no COI,[8,21] one had a statement regarding methods used to avoid potential COI,[3] two had a statement suggesting potential COI,[9,22] and two guidelines did not have COI statements available.[23,24] Literature search methodology description varied amongst the included guidelines with four guidelines lacking specificity to debridement related search terms,[3,8,21,22] two provided literature search methodology in a separate source,[23,24] and one set of guidelines did not have detailed literature search methods.[9] Other aspects of guideline development methodology were sufficiently described in three of the guidelines.[3,22,24] No identified guidelines were specific to debridement of DFUs, most guidelines had a broader focus on DFU,[8,9,22-24] and one had a broad focus on diabetes.[3] One guideline focused on CSWD and was not specific to DFU but had one recommendation specific to CSWD of DFUs.[21] Of the included guidelines with a broad focus, four provided an explicit scope and/or purpose.[8,22-24] The degree of stakeholder representation was outlined in two guidelines.[21,23] One suggested inclusive input from primary caregivers, public health, patients and industry,[23] while one incorporated stakeholder input from an online survey and facilitated discussions of guideline development panel members.[21] Another guideline specifically mentions that it scored lowest during guideline validation on stakeholder involvement (specifically patients) in addition to scoring low during validation on editorial independence.[22] None of the other guidelines provided an explicit statement of the limitations or results of recommendation validation. A summary of the critical appraisal of the included guidelines is available in Appendix 5, Table A5.4.

Summary of Findings

Major findings and author's conclusions regarding the clinical effectiveness evidence of DFU debridement are summarized in Appendix 6, Table A6.1.

The identified SR, Braun et al., 2014, summarizes the largest amount of evidence contained within this report.[14] This SR did not identify strong evidence to support surgical debridement effectiveness for the treatment of DFUs. Two SRs included in Braun et al., 2014 suggest that there is no significant benefit of surgical debridement over standard treatment. Another SR included in Braun et al., 2014 concludes that weak evidence supports the use of sharp debridement, and bases this conclusion on a subgroup analysis of a single RCT.[14] Conclusions regarding surgical debridement are tempered by the fact that the trials of the included SRs are small trials at a high risk of bias and lack replication.[7] Braun et al., 2014 found evidence from pooled data of three RCTs that hydrogels are statistically significantly more effective in healing DFUs than SWC. The primary studies supporting hydrogel debridement were of moderate to high risk of bias.[7,14] The included SR also found no evidence for increased clinical efficacy of MDT or hydrodebridement over SWC, although hydrodebridement did decrease wound debridement time.[14]

The included MA exclusively examined evidence for the clinical efficacy of MDT of DFUs.[17] When results were pooled from four studies there was no statistically significant benefit observed for MDT for outcome of proportion of DFU healed, however when one trial was left out of the analysis, a statistically significant clinical benefit of MDT was identified. The excluded trial defined complete healing differently, and a difference in this data was identified by a sensitivity analysis, based on leave-one-out cross validation.[17] There were no statistically significant differences in infection incidence between MDT and SWC in data pooled from two studies. The MA did find evidence of MDT clinical superiority in the outcomes of time to healing, amputation rate, and antibiotic usage. The authors concede that there is insufficient high-quality evidence available to make definitive conclusions.[17]

Two RCTs compared CCO to SMG treatment of DFUs.[19,20] Both studies found statistically significant improvements during the study in wound assessment scores for both CCO and SMG, however one study found a statistically significant improvement at an earlier time point with CCO.[20] One study found a statistically significant greater number of ulcers for which healing stalled and a greater requirement for surgical debridement in the SMG group.[20] Neither study observed any differences in the frequency of adverse events and neither found any adverse events to be treatment related.[19,20] The RCT examining hydrodebridement did not observe any statistically significant differences between groups for any outcomes examined.[18]

No clinical effectiveness evidence was identified specific to surgical callus debridement.

The findings of the economic study included in this report are summarized in Appendix 6, Table 6.2.

The included CEA reported that the average cost per responder was less for the CCO group than the SMG group in the physician's office and in the wound clinic facility. The average cost of selective sharp debridement was less in the CCO group in both settings while the evaluation and management costs were less in the control group in both settings. The CCO group required an average of twice as many visits for evaluation and management while the SMG required on average seven times as many selective sharp debridement procedures.[20]

Recommendations relevant to debridement of DFUs are summarized in Appendix 6, Table 6.3. Grades of recommendations and levels of evidence that are referenced in the following text are also summarized in Appendix 4.

The two Canadian guidelines were both published in 2013.[3,21] Rodd-Nielsen et al. recommended treating DFU with CSWD as part of a multimodal approach to optimal care. This recommendation was supported by a low level of evidence.[21] The recommendation from the CDA, graded Grade B, was that debridement of nonviable tissue in nonischemic wounds, in addition to offloading, is part of the general principles of wound management. A specific type of debridement is not part of this recommendation. The recommendation supported by the highest level of evidence is from ConvaTec published in 2013. This recommendation is for selecting autolytic debridement of DFUs with more than 25% necrotic tissue in the wound and is supported by an A level of evidence. For these wounds, ConvaTec also recommends selecting surgical or enzymatic debridement of such DFUs but with a level of evidence to support the recommendation of B and C, respectively.[22] Guidelines from the WOCN, published in 2012, recommend assessing for focal callus formation and routine debridement of focal calluses to decrease plantar pressures. This callus debridement recommendation was supported by a level of evidence of B.[8] The IDSA published four relevant recommendations in 2012, all are supported by a low level of evidence except for one supported by a moderate level of evidence. This best supported recommendation is also a strong graded recommendation that DFUs should receive appropriate wound care which usually consists of debridement aimed at removing debris, eschar, and surrounding callus.[9] These guidelines also have four additional strongly graded recommendations although the evidence to support them was evaluated as weak. These recommendations include: clinicians should debride any wound that has necrotic tissue or surrounding callus; clinicians should seek consultation from those with adequate training in wound debridement especially for extensive procedures; and in more complex or reconstructive cases the surgeon should have experience and adequate knowledge of foot anatomy. With regards to debridement methods for DFUs the IDSA also recommended that sharp (or surgical) methods are generally the best. This recommendation was assigned a strong

grade with a weak level of evidence to support it. Mechanical, autolytic, and larval debridement methods were recommended as appropriate for some DFUs, with a weak grade recommendation supported by a low level of evidence.[9] In 2011, NHMRC published a recommendation graded B that topical hydrogel dressings may be considered for autolytic debridement to assist the management of non-ischemic, non-healing ulcers with dry, non-viable tissue. These recommendations also include a recommendation graded as expert opinion that local sharp debridement of non-ischemic wounds should be performed as it improves ulcer healing.[24] The same year guidelines from NICE stated that the guideline development group agreed it was not appropriate to recommend specific debridement techniques because of the limited, low quality evidence. The only relevant recommendation in the NICE guidelines was graded as expert opinion and stated that debridement should only be done by healthcare professionals from a multidisciplinary foot care team, using the technique that best matches their specialist expertise, clinical experience, patient preference, and the site of the ulcer.[23]

Limitations

The interpretation of clinical effectiveness data from the included SR and MA is complicated by the use of different comparators in the examined trials. There was also an unclear risk of bias in many studies included in the SR and MA.[7] The possibility of publication bias was identified in the MA examining MDT of DFUs but was not assessed in any other included studies. The identified economic study evaluated costs outside of a Canadian setting and therefore may have limited applicability to a Canadian healthcare setting.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Despite a lack of evidence for clinical efficacy, surgical debridement is often part of standard care for DFUs.[7,9,14,19,20] Contrasting evidence was identified in this assessment on the efficacy of surgical debridement, and good-quality evidence for a beneficial clinical effect is lacking.[5-7,14] Contrasting evidence was also identified for the clinical effectiveness of MDT for DFUs. Pooled data from low-quality evidence in the included MA supported MDT superiority for DFU healing efficacy and healing rate in addition to requiring less amputation and antibiotic usage than SWC.[17] The included SR identified evidence that suggested MDT did not significantly improve healing or amputation risk.[14] The included SR identified data which found that hydrogels were a statistically significantly more effective treatment for DFUs as compared to SWC.[14] One of two open-label RCTs found a statistically significant improvement in the number of DFUs decreasing in surface area when treated with CCO as compared to SMG.[20] No clinical effectiveness evidence was identified for surgical callus debridement. Evidence identified in this report is consistent in finding that CCO and hydrogels may offer improved clinical outcomes in the debridement of DFUs, although the evidence is from RCTs with methodological limitations with moderate to high risk of bias.[7,14,19,20]

The CEA found a lower average cost per responder using CCO as compared to SMG. The lack of objective criteria for DFUs requiring surgical debridement in the control arm, a major source of cost difference, brings uncertainty to this conclusion.[20] No additional cost-effectiveness data was identified.

The identified guidelines were generally inconsistent with regards to recommendations for DFU debridement.[3,8,9,21-24] The two Canadian guidelines recommend debridement as part of a broader approach to optimal DFU treatment.[3,21] Three recommendations, based upon a low level of evidence, emphasize appropriate training, qualifications, and expertise for those

conducting DFU debridement procedures.[9,23] Three guidelines have recommendations to select autolytic hydrogel dressings for DFU debridement, however the strength of these recommendations varies considerably.[9,22,24] Two of these guidelines place a higher grade on a recommendation for the use of hydrogels than a recommendation for the use of surgical debridement.[22,24] Enzymatic debridement of DFUs is also recommended, and supported by a low level of evidence.[22] Three recommendations from two sets of guidelines mention callus debridement, however neither recommend surgical callus debridement specifically.[8,9] One of the callus debridement recommendations is aimed at DFU prevention by reducing focused plantar pressure.[8] The other guideline recommends that debridement of calluses be a part of DFU treatment.[9]

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

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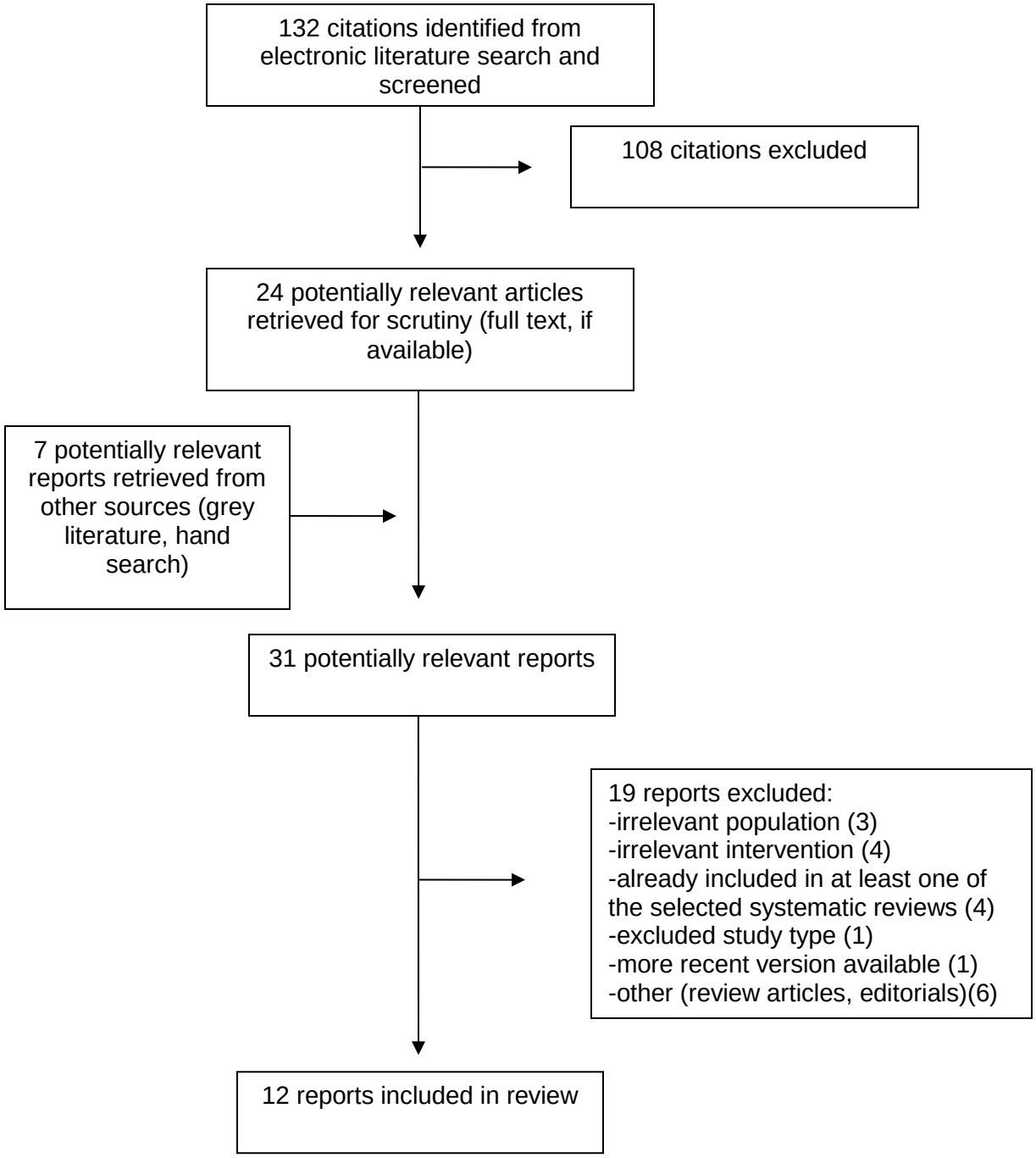
LIST OF ABBREVIATIONS

ACP	American College of Physicians
AGREE	Appraisal of Guidelines for Research and Evaluation
AHRQ	Agency for Healthcare Research and Quality
AMSTAR	Assessing the Methodological Quality of Systematic Reviews
AMWT	advanced moist wound care
CCO	clostridial collagenase ointment
CDA	Canadian Diabetes Association
CEA	cost-effectiveness analysis
COI	conflict of interest
CS	case-control study
CSWD	Conservative Sharp Wound Debridement
DFU	diabetic foot ulcer
DM	diabetes mellitus
GDG	guideline development group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HTA	health technology assessment
IDSA	Infectious Diseases Society of America
ITT	intention to treat
MA	meta-analysis
MDT	maggot debridement therapy
MD	mean days
NHMRC	National Health and Medical Research Council
NICE	National Institute for Health and Clinical Excellence
PCS	prospective case-control study
PICO	population, intervention, comparator, outcomes
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized controlled trial
RCS	retrospective case-control study
RR	relative risk
SD	standard deviation
SMG	saline moistened gauze
SR	systematic review
SWC	standard wound care
UK	United Kingdom
USA	United States of America

APPENDIX 1: Selection of Included Studies



APPENDIX 2: SUMMARY OF INCLUDED STUDIES

Table A2.1: Trials/SRs/Guidelines Included in Identified Studies

		SR				Trials											
		Game et al., 2012[38]	Edwards et al., 2010[7]	Lebrun et al., 2010[5]	Hinchliffe et al., 2008[6]	Cardinal et al., 2009[29]	Paul et al., 2009[33]	Caputo et al., 2008[32]	Piaggesi et al., 2003[28]	Saap et al., 2002[27]	Whalley et al., 2001[34]	Markevich et al., 2000[35]	D'Hemecourt et al., 1998[36]	Jensen et al., 1998[31]	Piaggesi et al., 1998[30]	Vandeputte et al., 1997[37]	Steed et al., 1996[26]
Identified SRs	Braun et al., 2014[14]	X	X	X	X												
	Brolman et al., 2012[15]		X														
	Game et al., 2012[38]						X	X									
	Hunt et al., 2011[16]		X														
	Edwards et al., 2010[7]										X	X	X	X	X	X	
	Lebrun et al., 2010[5]					X			X	X					X		X

APPENDIX 3: SUMMARY OF STUDY CHARACTERISTICS

Table A3.1: Summary of Study Characteristics of Included SRs/MAs/RCT

Study Design	Population (sample size)	Intervention	Comparator(s)	Outcomes
Braun et al., 2014[14]				
SR: DFU (4 SRs)	DFU	Debridement (Hydrogels, Larvae therapy, Sharp debridement, Versajet® hydrodebridement) + other DFU therapies not related to debridement	SWC	• DFU healing efficacy • Time to heal
Tian et al., 2013[17]				
MA: (1 RCT, 1 RCS, 1 PCS, 1 CS)	DFU (n=282)	MDT, MDT with *L.cuprina* and subcutaneous insulin	Hydrogel, SWC, surgical debridement and subcutaneous insulin	• DFU healing efficacy • Time to heal • Antibiotic usage • Amputation • Infection incidence
Tallis et al., 2013[20]				
RCT and CEA (See Appendi 3, Table A3.2) 12 weeks	Neuropathic DFU between 0.5 and 10cm^2 (n=48)	Selective sharp debridement and CCO with off-loading	Selective sharp debridement and SMG with off-loading	• Wound assessment • Change in ulcer size (area) • Adverse events • Health economic outcomes (See Appendix 3, Table A3.2)
Motely et al., 2014[19]				
RCT 12 weeks	Neropathic, nonischemic DFU (n=55)	Selective sharp debridement and CCO with off-loading	Selective sharp debridement and SMG with off-loading	• Wound assessment • Change in ulcer size (area) • Time to heal • Adverse events
Bowling et al., 2011[18]				
RCT 4 weeks	Nonclinically infected DFU with necrotic tissue (n=20)	Jet lavage debridement with superoxidized aqueous saline (Dermacyn,	Jet lavage debridement with standard saline	• Ulcer bacterial load • Change in ulcer size (area) • Adverse events • Reduction in necrotic tissue

Study Design	Population (sample size)	Intervention	Comparator(s)	Outcomes
		Oculus Innovative Sciences Inc, Petaluma, CA)		

CCO=clostridial collagenase ointment; **CEA**=cost-effectiveness analysis; **CS**=case-control study; **DFU**=diabetic foot ulcer; **MA**=meta-analysis; **MDT**=maggot debridement therapy; **PCS**=prospective case-control study; **RCS**=retrospective case-control study; **RCT**=randomized controlled trial; **SMG**=saline moistened gauze; **SWC**=standard wound care

Table A3.2: Summary of Study Characteristics of Included Economic Analyses

Type of Economic Evaluation, Perspective, Time	Patient Population	Comparison	Outcomes	Assumptions
Tallis et al., 2013[20]				
CEA Centers for Medicare and Medicaid Services (USA) as a payer 12 weeks	Neuropathic DFU (n=48)	Selective sharp debridement with off-loading combined with CCO vs SMG	• Cost per responder • Selective sharp debridement costs • Evaluation and Management costs • Costs for different settings: Physician Office and Wound Care Facility	Costs for DFU cover dressings were equal between groups No cost discounting CCO use estimated based upon proper, not actual, usage data

CCO=clostridial collagenase ointment; **CEA**=cost-effectiveness analysis; **DFU**=diabetic foot ulcer; **SMG**=saline moistened gauze; **USA**=United States of America

Table A3.3: Summary of Study Characteristics of Included Guidelines

Origin, Publication Year	Interventions of Interest	Grading (See Appendix 3)	Target Users
ConvaTec 2013[22] (based on AHRQ summary)			
ConvaTec. SOLUTIONS® wound care algorithm, Agency for Healthcare Research and Quality USA, 2013	Debridement: autolytic, enzymatic, surgical, other	Levels of Evidence I – VI Recommendations Graded A - C	Advanced Practice Nurses Allied Health Personnel Health Care Providers Nurses Physical Therapists Physician Assistants Physicians Podiatrists
Rodd-Nielsen et al., 2013[21]			
Canadian Association for Enterostomal Therapy, Conservative Sharp Wound Debridement Evidence-Based Recommendations, Canada, 2013	CSWD	Levels of Evidence Ia – IV	Nurses
CDA 2013[3]			
Canadian Diabetes Association, Clinical Practice Guidelines Expert Committee, Canada, 2013	Debridement	Levels of Evidence 1A – 4 Recommendations Graded A - D	Healthcare professionals
WOCN 2012[8] (Based on AHRQ summary)			
Wound, Ostomy, and Continence Nurses Society, Agency for Healthcare Research and Quality USA, 2012	Debridement: hydrogels	Levels of Evidence I – VI Recommendations Graded A - C	Advanced practice nurses Allied Health Personnel Dietitians Health Care providers Nurses Physical Therapists Physician Assistants Physicians Podiatrists

Origin, Publication Year	Interventions of Interest	Grading (See Appendix 3)	Target Users
IDSA 2012[9]			
Infectious Diseases Society of America, USA, 2012	Debridement: surgical, mechanical, autolytic and larval therapy	Levels of Evidence High, Moderate, Low and Very Low quality evidence ratings Recommendations Graded Strong or Weak	Clinicians Healthcare organizations
NHMRC 2011[24]			
National Health and Medical Research Council, Melbourne, Australia, 2011	Debridement: sharp, hydrogel, autolytic, larval therapy	Levels of Evidence I – IV Recommendations Graded A -D	Broad range of Health Professionals and Healthcare Workers in urban and rural/remote primary care and specialist foot centres
NICE 2011[23]			
National Health Service, National Institute for Health and Clinical Excellence, London, UK, 2011	Debridement: surgical, hydrogel, larval	GRADE evidence profiles	Hospital staff who care for patients with diabetic foot problems

AHRQ=Agency for Healthcare Research and Quality; **CDA**=Canadian Diabetes Association; **CSWD**=Conservative Sharp Wound Debridement; **GRADE=**Grading of Recommendations Assessment, Development and Evaluation; **IDSA**=Infectious Diseases Society of America; **NHMRC**= National Health and Medical Research Council; **NICE**=National Institute for Health and Clinical Excellence; **UK**=United Kingdom; **USA**=United States of America; **WOCN**=Wound, Ostomy and Continence Nurses Society

APPENDIX 4: Summary of Guideline Grading and Recommendations and Levels of Evidence

Table A4: Guideline Grading of Recommendations and Levels of Evidence

Recommendation	Levels of Evidence
ConvaTec 2013[22] (based on AHRQ summary)	
A Two or more supporting RCTs (Level **I** or **II**), an MA of RCTs, or Cochrane SR of RCTs **B** One or more supporting controlled trials (n≥10), or two or more supporting non-RCTs (n≥10) (Level **III**) **C** Two supporting case series (n≥10) or expert opinion	**I** Statistically significant difference (p<0.05) from an RCT **II** An RCT not meeting Level I criteria **III** A non-RCT **IV** Retrospective cohort or case series (n≥10) **V** Case series (n≥10) with no controls **VI** Case report (n≤10)
Rodd-Nielsen et al., 2013[21]	
N/A	**Ia** Evidence from MA or SR of RCTs **Ib** Evidence from one or more RCTs **IIa** Evidence from one or more well-designed controlled studies lacking randomization **IIb** Evidence from one or more well-designed quasi-experimental study without randomization **III** Evidence from well-designed comparative studies, correlation studies and case studies **IV** Evidence from reports or opinions of expert committees, and/or clinical experience of respected authorities
CDA 2013[3]	
A Evidence from Level **1** **B** Evidence from Level **2** **C** Evidence from Level **3** **D** Evidence from Level **4** or consensus	**1A** SR or MA of high quality RCTs **1B** non-RCT or cohort study with indisputable results **2** moderate quality RCT or SR **3** non-RCT or cohort study or SR, MA of Level 3 studies **4** Other
WOCN 2012[8] (based on AHRQ summary)	
A Two or more supporting RCTs (Level **I** or **II**), an MA of RCTs, or Cochrane SR of RCTs **B** One or more supporting controlled trials (n≥10), or two or more supporting non-RCTs (n≥10) (Level **III**) **C** Two supporting case series (n≥10) or expert opinion	**I** Statistically significant difference (p<0.05) from an RCT **II** An RCT not meeting Level I criteria **III** A non-RCT **IV** Retrospective cohort or case series (n≥10) **V** Case series (n≥10) with no controls **VI** Case report (n≤10)
IDSA 2012[9]	
Strong Desirable effects clearly outweigh undesirable effects, or vice versa **Weak** Desirable effects closely balanced with undesirable	**High-quality** Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies **Moderate-quality** Evidence from moderate quality RCTs or exceptionally strong evidence from unbiased

Recommendation	Levels of Evidence
effects, or uncertainty in estimates	observational studies **Low-quality** Evidence for at least one critical outcome from observational studies or indirect evidence or poor quality RCTs or indirect evidence **Very low-quality** One critical outcome evident in clinical observations or very indirect evidence
NHMRC 2011[24]	
A Level **I** (n≥1) or Level **II** (n≥2) with a low risk of bias **B** Level **II** (n≤2) with a low risk of bias or SR or several level **III** studies with low bias risk **C** Level **III** (n≤2) with low bias risk or Level **I** or **II** studies with moderate bias risk **D** Level **IV** (n≥1) or Level **I** – **III**, SRs with high bias risk **EO** Expert Opinion	**I** SR of Level **II** **II** RCT **III-1** pseudo-randomized controlled trial **III-2** non-RCT, cohort study, case-control study, interrupted time series with control group **III-3** historical control study, two or more single arm studies, or interrupted time series without parallel control group **IV** Case series
NICE 2011[23]	
N/A	<u>GRADE evidence profile</u> **High** - RCT **Moderate** **Low** **Very Low** – Observational study <u>Level decreases one category for:</u> Study limitations Inconsistency Indirectness Imprecision Publication bias <u>Level increases one category for:</u> Large magnitude of effect Evidence of dose-response All plausible confounding factors are accounted for

AHRQ=Agency for Healthcare Research and Quality; **CDA**=Canadian Diabetes Association; **GRADE**=Grading of Recommendations Assessment, Development and Evaluation; **IDSA**=Infectious Diseases Society of America; **MA**=meta-analysis; **N/A**=not applicable; **NHMRC**=National Health and Medical Research Council; **NICE**=National Institute for Health and Clinical Excellence; **RCT**=randomized controlled trial; **SR**=systematic review; **UK**=United Kingdom; **USA**=United States of America; **WOCN**=Wound, Ostomy and Continence Nurses Society

APPENDIX 5: Summary of Critical Appraisal

Table A5.1: Critical Appraisal Summary for SR and MA using AMSTAR tool[10]

Strengths	Limitations
Braun et al., 2014[14]	
• COI statement • Literature search selection/inclusion/exclusion methodology outlined • PRISMA flowchart • Study quality assessed • Data extraction methodology outlined • Tabulated study conclusions	• One author with financial COI • Lacks pre-defined research questions • No mention of COI statements of included studies • Unquantified conclusions • No assessment of publication bias • No assessment of patient characteristics • No mention of adverse events
Tian et al., 2013[17]	
• Statement of no financial COI • Literature search selection/inclusion/exclusion methodology detailed done in duplicate • PRISMA flowchart • Predefined objective using PICO • Risk of bias of included studies assessed • Statistical methods described • Statistical heterogeneity tested • Statistical test for publication bias • Sensitivity analysis conducted • Quantified conclusions • Explicit discussion of limitations	• No examination of adverse events • Analysis suggests possibility of publication bias exists in the included trials • Included studies had small sample size, differences in patient classification and methods • Only one included study was an RCT and it had risk of selection, performance, and detection bias
COI=conflict of interest; **PICO**=population, intervention, comparator, outcomes; **PRISMA**=Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **RCT**=randomized controlled trial;	

Table A5.2: Critical Appraisal Summary for included RCTs using Downs and Black checklist[11]

Strengths	Limitations
Tallis et al., 2013[20]	
• Registered clinical trial • Clear patient eligibility criteria • Well described interventions, outcomes and outcome assessment methods • Patient and ulcer characteristics tabulated • Randomization method outlined • Statistical power determined a priori to determine the number of patients required • Statistical methods described using ITT analysis • COI statement • Adverse event outcomes presented	• Industry sponsored study (Healthpoint Biotherapeutics Ltd., Fort Worth, TX) • Open-label trial • No data for decision on or criteria for debridement
Motely et al., 2014[19]	
• Registered clinical trial • Well described wound assessment tool • Clear patient eligibility criteria • Patient and ulcer characteristics tabulated • Randomization method outlined • Statistical methods described using ITT analysis • Interventions, outcomes and outcome assessment described • Adverse event outcomes presented	• Industry sponsored study (Healthpoint Biotherapeutics Ltd., Fort Worth, TX) • Open-label trial • No statistical power calculations • No COI statement - industry identified on clinicaltrials.gov • No data for decision on or criteria for debridement
Bowling et al., 2011[18]	
• COI statement • Patient and ulcer characteristics tabulated • Clear patient eligibility criteria • Randomization method outlined • Adverse event outcomes mentioned	• Industry sponsored study • No allocation concealment and blinding of assessment methods described • Outcomes of uncertain or indirect clinical relevance • Undescribed outcome assessment
COI=conflict of interest; **ITT**=intention to treat;	

Table A5.3: Critical Appraisal Summary for Economic Studies using Drummond checklist[12]

Strengths	Limitations
Tallis et al., 2013[20]	
• Well defined analysis • Clear purpose • Relevant comparator • Economic evaluation of an RCT • Cost breakdown provided with source • Patient characteristics tabulated	• Limited long term data and endpoints • RCT was open-label trial • No sensitivity analysis performed
RCT=randomized controlled trial	

Table A5.4: Critical Appraisal Summary for Guidelines using AGREE II tool[13]

Strengths	Limitations
ConvaTec 2013[22] (based on AHRQ summary)	
• Graded recommendations • Grades of recommendations linked to a level of evidence • Guideline development methodology described • COI statement • Benefits and harms of guideline implementation outlined • Explicit scope	• No patient stakeholder involvement in guideline development • One participant had a conflict of interest • Broad focus • Literature search methodology lacks specificity to debridement of DFU, and lacks inclusion and exclusion criteria • No statement of limitations
Rodd-Nielsen et al., 2013[21]	
• Recommendations linked to a level of evidence • Canadian perspective • Statement of no COIs	• Recommendations not graded • Literature search methodology lacks detail and specificity to debridement of DFU • Unclear representative stakeholder involvement • No statement of limitations
CDA 2013[3]	
• Graded recommendations explicitly linked to evidence level • Guideline development methodology described • Statement regarding avoidance of potential COIs • Guideline update process outlined • Target audience described • Canadian perspective	• Very broad focus • Literature search methodology lacks specificity to debridement of DFU • No detailed description of stakeholder representation • No statement of limitations
WOCN 2012[8] (based on AHRQ summary)	
• Graded recommendations • Grades of recommendations linked to a level of evidence • Statement of no COIs • Explicit scope • Benefits and harms of guideline implementation outlined	• Broad focus • Literature search methodology lacks specificity to debridement of DFU, inclusion and exclusion criteria • No description of stakeholder representation • No statement of limitations
IDSA 2012[9]	
• Graded recommendations explicitly linked to evidence level • COI statement	• Broad focus • Full text of methodology not available • No description of stakeholder representation • No statement of limitations • Potential COI in statement
NHMRC 2011[24]	
• Graded recommendations • Grades of recommendations linked to a level of evidence • Literature search methodology provided in separate source	• Broad focus • COI statement only available in external document • No procedure for limiting potential COIs • No statement of limitations

Strengths	Limitations
• Quality of supporting literature evaluated and discussed • Explicit scope and purpose • Guideline development methodology described • Guideline update process outlined • Guidance for guideline implementation • Suggestions for needed future research	
NICE 2011[23]	
• Explicit scope • Guideline update process outlined • Guidance for guideline implementation • Stakeholder involvement in guideline development • Literature search methodology described in separate source	• Broad scope • Recommendations not graded • Evidence quality evaluated only for individual studies •Evidence quality not presented with recommendations • No COI statement available • No statement of limitations

AHRQ=Agency for Healthcare Research and Quality; **CDA**=Canadian Diabetes Association; **COI**=conflict of interest; **DFU**=diabetic foot ulcer; **IDSA**=Infectious Diseases Society of America; **NHMRC**=National Health and Medical Research Council; **NICE**=National Institute for Health and Clinical Excellence; **WOCN**=Wound, Ostomy and Continence Nurses Society

APPENDIX 6: Summary of Findings

Table A6.1: Summary of Main Findings and Author's Conclusions of SRs/MAs/RCTs

Main Findings	Author's Conclusions
Braun et al., 2014[14]	
Edwards et al., 2010[7] 6 RCTs (n=31-172) 1) "Hydrogels significantly more effective in healing DFUs" (pp. 269) RR>1 favours hydrogels RR (95%CI): 1.84 (1.30, 2.61) 2) "Surgical debridement showed no significant benefit over standard treatment" (pp. 269) Lebrun et al., 2010[5] 5 trials (n=20-241) "No significant benefit of surgical debridement over SWC based on limited evidence" (pp. 269) Hinchliffe et al., 2008[6] 3 studies "Weak evidence supports the use of sharp debridement based on a subgroup analysis of a single RCT" (pp. 269) Game et al., 2012[38] 2 studies 1) "Larvae therapy did not significantly improve healing or amputation risk" (pp. 269) 2) "Versajet® decreased wound debridement time but did [not] increase proportion of wounds healed at 12 weeks" (pp. 269)	"Four systematic reviews concluded that good-quality evidence for a beneficial effect of [surgical] debridement on ulcer healing is lacking." (pp. 276) "A Cochrane review evaluated the evidence for different types of debridement, including autolytic debridement, enzymatic debridement, and larval therapy, and found that autolytic debridement with hydrogels was superior to standard wound care, based on differences in healing rates" (pp. 276)
Tian et al., 2013[17]	
Proportion of DFU Healing (4 trials) - No Significant Difference RR>1 favours MDT RR (95%CI (*p*)): 1.33 (0.94, 1.88 (*p*=0.11)) (I^2=29%) Leaving one RCT out - sensitivity analysis - leave-one-out cross validation **Proportion of DFU Healing (3 trials)** RR>1 favours MDT RR (95%CI (*p*)): 1.80 (1.07, 3.02 (*p*=0.03)) (I^2=NR) **Time to Healing (2 trials)** MD<0 favours MDT MD (95%CI (*p*)): -3.70 (-5.76, -1.64 (*p*=0.0004)) (I^2=0%) **Amputation Rate (2 trials)** RR<1 favours MDT	"There is insufficient high-quality evidence available in the current literature regarding the effectiveness of MDT for the treatment of DFUs. Hence, the findings from this meta-analysis are by no means definitive. Nevertheless, the findings suggest that MDT may be more effective in increasing healing rate and antibiotic-free days,

Main Findings	Author's Conclusions
RR (95%CI (*p*)): 0.41 (0.20, 0.85 (*p*=0.02)) (I^2=0%) **Infection Incidence (2 trials) - No Significant Difference** RR<1 favours MDT RR (95%CI (*p*)): 0.82 (0.65, 1.04 (*p*=0.10)) (I^2=0.0%) **Antibiotic Usage (2 trials)** Mean number of antibiotic-free days (± SD) (*p*=0.001) MDT: 126.8 (± 30.3) Control: 81.9 (± 42.1)	and decreasing rate of amputation and time to healing compared with control interventions." (pp. 469)
Tallis et al., 2013[20]	
Wound Assessment Scores No statistically significant differences between CCO and SMG groups for any timepoints. Both groups had clinically relevant, statistically significant improvements from baseline. CCO group showed statistically significant improvement at week 1, while SMG did not show statistically significant improvement until week 2. **Change in Ulcer Surface Area** Change between groups not tested for statistical significance. CCO mean percent change from baseline EOT: -44.9% (*p* = 0.016) EOS: -53.8% (*p* = 0.012) SMG mean percent change from baseline (not statistically significant) EOT: +0.8% EOS: +8.1% **Change in Ulcer Surface Area Response Rate EOS** Large response (≥50% reduction from baseline) CCO: 67% SMG: 71% Moderate response (>10%, <50% reduction from baseline) CCO: 25% SMG: 4% Stalled (≤10% or increase in size from baseline) (*p* < 0.05) CCO: 8% SMG: 25% **Surgical Debridement Requirement** Mean number of medically necessary surgical debridements as determined by investigator - EOS (*p* = NR) CCO: 1 (baseline debridement) SMG: 6.9 **Adverse Events**	"The clinical utility of CCO is better or comparable to that of standard of care with SMG plus weekly sharp debridement. Significant improvement in wound bed appearance was obtained more rapidly with CCO therapy than SMG therapy. In addition, CCO-treated DFUs had an enhanced rate of healing during the treatment period and for several weeks after the cessation of treatment, whereas the SMG therapy had no effect. Moreover, the clinical benefits with CCO accrued in the absence of additional surgical debridement, whereas patients in the SMG group continue to require surgical debridement during follow-up." (pp. 1818)

Main Findings	Author's Conclusions
No differences between groups observed. None of the reported adverse events were assessed as being related to DFU treatment.	
Motely et al., 2014[19]	
Wound Assessment Scores No statistically significant differences between CCO and SMG groups for any timepoints. Both groups had clinically relevant, statistically significant improvements from baseline. **Change in Ulcer Surface Area** Change between groups not statistically significant. CCO mean percent change from baseline EOT: -68% ($p < 0.001$) EOS: -61% ($p < 0.001$) SMG mean percent change from baseline (not statistically significant) EOT: -36% EOS: -46% **Surgical Debridement Requirement EOS** No statistically significant differences between groups **Time to Closure EOS** Median time to closure (statistical significance NR) CCO: 9 weeks SMG: 11 weeks **Adverse Events EOS** Total number of adverse events (not statistically significant) No events were determined to be related to treatment CCO: 20 SMG: 18	"Enzymatic debridement with CCO in conjunction with serial sharp debridement appeared to provide a benefit beyond what can be achieved using serial sharp debridement with standard care alone. In addition, it seems desired outcomes may be achieved more rapidly when using CCO with sharp debridement than when using CCO alone." (pp. 14/15)
Bowling et al., 2011[18]	
No statistically significant difference were observed for any outcome. **Adverse Events** None observed in either groups	"No significant differences in the reduction of bacterial load and wound size between groups were observed at week 4 of treatment versus baseline. It may be that the hydrodebridement device itself was an efficient debrider and that the constitution of the replacement

Main Findings	Author's Conclusions
	solution was of little consequence. Larger and longer clinical trials are needed to confirm the results of this pilot study." (pp. 126)
CCO=clostridial collagenase ointment; **EOS**=end of study; **EOT**=end of treatment; **DFU**=diabetic foot ulcer; **MD**=mean days; **MDT**=maggot debridement therapy; **NR**=not reported; **RCT**=randomized controlled trial; **SD**=standard deviation: **SMG**=saline moistened gauze	

Table A6.2: Main Study Findings and Author's Conclusions of Economic Studies

Main Findings	Author's Conclusions
Tallis et al., 2013[39]	
Cost per responder (US $) Physician Office Average (range) CCO: $832 (829 - 1021) SMG: $1042 (825 - 1260) Wound Clinic Facility Average (range) CCO: $1607 (1601 - 1794) SMG: $1980 (1170 - 2189) **Selective sharp debridement costs** (US $) Physician Office Average (range) CCO: $75 (75 - 150) SMG: $527 (150 - 903) Wound Clinic Facility Average (range) CCO: $129 (129 - 257) SMG: $901 (257 - 1544) **Evaluation and Management costs** (US $) Physician Office Average (range) CCO: $511 (468 - 511) SMG: $255 (43 - 468) Wound Clinic Facility Average (range) CCO: $1168 (1070 - 1168) SMG: $584 (97 - 1070)	"Although delivering similar or better clinical outcomes, depending on the clinical assessment used, enzymatic debridement of DFUs with CCO offers better value compared with the SMG regardless of the ambulatory care setting. In particular, CCO therapy is a cost-effective method of debridement in the management of patients with DFUs." (pp. 1818)
CCO=clostridial collagenase ointment; **DFU**=diabetic foot ulcer; **SMG**=saline moistened gauze;	

Table A6.3: Summary of Recommendations by Source (see Appendix 3 for grading schemes).

ConvaTec 2013[22] (based on AHRQ summary)
Recommendation: Debride diabetic foot ulcers with more than 25% necrotic tissue in the wound allowing professionals to select among these options: a. Autolytic **Level of Evidence = A** b. Enzymatic **Level of Evidence =C** c. Surgical **Level of Evidence =B**
Rodd-Nielsen et al., 2013[21]
Recommendation: "Treat diabetic foot ulcers with CSWD as part of a multimodal approach to optimal care." **Level III** (pp. 250)
CDA 2013[3]
Recommendation: "General principles of wound management involve the provision of a moist wound environment, debridement of nonviable tissue (nonischemic wounds) and offloading of pressure areas." **Grade B** (pp. S148)
WOCN 2012[8] (based on AHRQ summary)
Recommendation: "Assess for focal callus formation, particularly over bony prominences or foot deformities. Routine debridement of focal calluses decreases plantar pressures." **Level of Evidence = B**
IDSA 2012[9]
Recommendation: "Clinicians should debride any wound that has necrotic tissue or surrounding callus; the required procedure may range from minor to extensive (**strong, low**)." (pp. 1680) "Clinicians without adequate training in wound debridement should seek consultation from those more qualified for this task, especially when extensive procedures are required (**strong, low**)." (pp. 1681) "Although most qualified surgeons can perform an urgently needed debridement or drainage, we recommend that in DFI cases requiring more complex or reconstructive procedures, the surgeon should have experience with these problems and adequate knowledge of the anatomy of the foot (**strong, low**)." (pp. 1683) "Diabetic patients with a foot wound should receive appropriate wound care, which usually consists of the following: a. Debridement, aimed at removing debris, eschar, and surrounding callus (**strong, moderate**). Sharp (or surgical) methods are generally best (**strong, low**), but mechanical, autolytic, or larval debridement techniques may be appropriate for some wounds (**weak, low**)." (pp. 1683)
NHMRC 2011[24]
Recommendation: "Local sharp debridement of non-ischaemic wounds should be performed as it improves ulcer healing." **Grade EO** (pp. 6) "Topical hydrogel dressings may be considered for autolytic debridement to assist the management of non-ischaemic, nonhealing ulcers with dry, non-viable tissue." **Grade B** (pp. 6)
NICE 2011[23]
"The GDG agreed that because the evidence was limited and of low quality, it was not appropriate to recommend specific techniques for debridement." (pp. 79)

Recommendation: "Debridement should only be done by healthcare professionals from the multidisciplinary foot care team, using the technique that best matches their specialist expertise, clinical experience, patient preference, and the site of the ulcer." **Expert opinion** (pp. 81)
AHRQ=Agency for Healthcare Research and Quality; **CDA**=Canadian Diabetes Association; **CSWD**=conservative sharp wound debridement; **DFI**=diabetic foot infections; **EO**=expert opinion; **GDG**=guideline development group; **IDSA**=Infectious Diseases Society of America; **NHMRC**= National Health and Medical Research Council; **NICE**=National Institute for Health and Clinical Excellence; **RCT**=randomized controlled trial; **WOCN**=Wound, Ostomy and Continence Nurses Society